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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Coutre, Steven
INTERNATIONAL APPLICATION NO: PCT/EP2004/006562
FILED: June 17, 2004
U.S. APPLICATION NO: 10/560669
35 USC §371 DATE: March 23, 2007
FOR: Pharmaceutical Uses of Staurosporine Derivatives

Art Unit: 1627
Examiner: Jean-Louis, Samira JM

MS: Appeal Brief- Patents
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Sir:

This is a Reply Brief filed in response to the Examiner's Answer dated September 29, 2010. The Commissioner is hereby authorized to charge any fees which may be required to Deposit Account No. 19-0134 in the name of Novartis.

ARGUMENT

Appellant responds to items 1 and 2 in the Response to Argument section found on pages 12-16 of the Examiner's Answer as follows:

(1) The presently claimed invention relates to the treatment of mastocytosis. Goekjian et al discloses that midostaurin effectively inhibits wild-type KIT. However, this reference is not relied on as disclosing that midostaurin would effectively inhibit the activated KIT, particularly the D816V mutant KIT, associated with mastocytosis. Instead, the Examiner relies on Longley et al as the basis to assert that the skilled artisan would expect "that any amount of reduction in Kit's phosphorylation by such compound would be useful in attenuating the effects of mastocytosis."

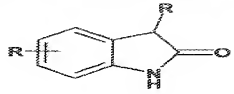
However, Longley et al does not contain any disclosure that supports such a conclusion. Moreover, the disclosure of Ma et al clearly demonstrates that the authors expect that only KIT inhibitors with significant activity against D816V mutant KIT would have utility for treating mastocytosis. Ma et al reports on experiments done with imatinib (STI571) and SU9529. The reference reports that both KIT inhibitors inhibit wild-type kit, but that neither significantly inhibits the D816V mutant KIT associated with SAHM (sporatic adult human mastocytosis). Based on these experiments, Ma et al concludes "These studies suggest that currently available KIT inhibitors may be useful in treating neoplastic cells expressing KIT activated by its natural ligand or by RT activating mutations such as gastrointestinal stromal tumors but that neither compound is likely to be effective against SAHM." See, the Abstract.

Based on the discussion above, Appellant asserts that the cited prior art does not support the Examiner's position "that any amount of reduction in Kit's phosphorylation by such compound would be useful in attenuating the effects of mastocytosis." In addition, Appellant asserts that the cited references do not provide any basis for the skilled artisan to expect midostaurin to significantly inhibit D816V mutated KIT.

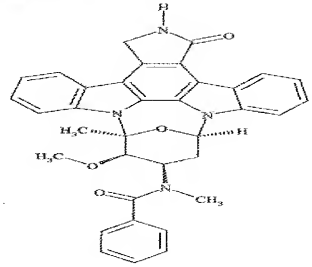
(2) The Examiner argues that the skilled artisan "would have indeed found it obvious to try the indolinone derivative of Goekjian to treat mastocytosis since Longley demonstrated that indolinone derivatives were effective in inhibiting both wild type KIT and mutant ones as well." However, Longley et al teaches that only one of five of the indolinone compounds tested substantially reduced KIT phosphorylation in the P-815 cell line, which express canine KIT that is considered equivalent to D816V human KIT. See, pages 692-693.

The Examiner also contends that "a finite number of solutions were indeed provided as Longley teaches the use of indolinone derivatives to inhibit phosphorylation of KIT and thus treat the disease." It is not clear to the Appellant how this provides a finite number of solutions which includes midostaurin unless the Examiner is asserting that midostaurin is so structurally similar to Longley et al's indolinone compounds that the skilled artisan would expect it to possess similar properties.

Based on information provided in Ma et al, *Journal of Investigative Dermatology*, (2000) 114, 392-394, which appears to disclose the same experiments as Longley et al, Appellant believes that Longley et al's indolinone compounds are the 3-substituted-2-indolinone compounds: 3-[4-Methyl-2-(2-oxo-1,2-dihydro-indol-3-ylidene-methyl)1H-pyrrol-3-yl]-propionic acid (SU5402) , 4-[4-(2-Oxo- 1,2-dihydro-indol-3-ylidenemethyl)-phenyl]-piperazine-1-carbaldehyde (SU4984), 3-[4-Methyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid (SU6663), 3-[5-(6-Methoxy-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-4-methyl-1H-pyrrol-3-yl]-propionic acid (SU6577), and 5-Chloro-3-(3,5-dimethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-indol-2-one (SU5614), which have the following general structure:



Appellant asserts that such indolinone derivatives are not structurally similar to complex staursporine derivatives, such as midostaurin:



Moreover, as discussed above, only one of the five indolinone derivatives tested by Longley et al substantially reduced KIT phosphorylation in the P-815 cell line. Thus, even

assuming, *arguendo*, that midostaurin is structurally similar to Longley et al's indolinone derivatives, there is no basis to reasonably expect that it would inhibit D816V mutated KIT at levels useful to treat mastocytosis.

Entry of this Reply Brief and consideration of the arguments presented herein are requested.

Respectfully submitted,

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